TITLE:

COHORT PROFILE UPDATE: THE ISLE OF WIGHT WHOLE POPULATION BIRTH COHORT (IOWBC)

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The original (Isle of Wight) Cohort

The Isle of Wight birth cohort (IOWBC) was established with support from the Isle of Wight Health Authority and subsequently supported by Asthma UK, National Institutes of Health (US) and the Medical Research Council (UK).[1] IOWBC is a whole population prospective, observational study investigating prevalence, natural history and risk and protective factors for the development of asthma and allergic diseases. All children (n=1536) born on the Isle of Wight between January 1989 and February 1990 were enrolled. Participants have been assessed 6 times since birth up to the age of 26 years. A wide range of phenotypic and environmental information has been collected using questionnaires and hospital medical records, study procedures, genetic and epigenetic assessments and over 10,000 biological samples have been collected.

The new focus (3rd Generation cohort)

Recent evidence indicates that grand parental health status and exposures, e.g., to smoking, or undesired nutritional intake can adversely influence health outcomes in grandchildren.[2-5] Thus, the risk to individual's health should consider not only parental genetics and exposures, but also cross-generational (intergenerational and transgenerational) influences.[6] This improved understanding could help formulate public health strategies.[7]

To gain a better understanding of the natural history and risk factors for asthma, allergic diseases and lung function over three generations, the Isle of Wight 3rd Generation (IOW 3rd Gen) cohort was established. An important focus in this cohort is the role of in utero exposures versus genetic inheritance to investigate transgenerational risk of asthma and allergy. The aim is to investigate;

- environmental exposures during pregnancy that impact epigenetic marks at birth
- the association of epigenetic (genome-wide methylation), with allergic diseases

- the extent to which methylation levels at CpG (cytosine-phosphate-guanine) sites are vertically transmitted from parents to offspring and contribute to inheritance of medical conditions
- the role of the microbiome in the development of asthma and allergy

Addressing these questions could critically impact on the prevention and treatment of asthma and allergies.

Both the original (IOWBC) and the IOW 3rd Gen are based at the David Hide Asthma and Allergy Research Centre on the Isle of Wight (IOW), United Kingdom (UK). The IOW is an island off the south coast of England with a resident population of 138,000. A 5-year project grant in 2010 from the National Institute of Allergy & Infectious Diseases helps establish the IOW 3rd Gen cohort providing support for recruitment of IOWBC participants (as parents), their partners and their children as well as assessment at 3 and 12 months for asthma and allergy. A follow-up grant from the National Heart Lung & Blood Institute allowed assessments at 3 and 6 years.

Who is in the cohort?

The IOW cohorts are largely Caucasian (98%) and include three generations: 1st generation (grandparents, F0) n=1536, the 2nd generation (Isle of Wight Birth cohort (IOWBC); n=1456) born 1989-90,[1] and the 3rd generation (children of IOWBC participants, IOW 3rd Gen; n=530) (born 2010 – current). The 1st generation (F0) were enrolled at the time of childbirth (F1-generation) and data and samples were collected to assess asthma and allergic status. Starting at birth, the F1-generation (IOWBC) has been assessed extensively and repeatedly for asthma and allergies up to the age of 26 years.[1]

Since 2010, 530 3rd generation children (born to F1-generation) have been enrolled. For the recruitment of the 3rd generation (F2-generation) during pregnancy, permission was obtained from

the National Research Ethic Service Committee South Central - Hampshire B (09/H0504/129) committee to consent mothers and fathers for their assessment and follow-up of their offspring at 3, 6 and 12 months. Approval was granted for further assessments of F2-children at 2 years (REC no.14/SC/0133), 3 years (REC no. 14/SC/1191), and 6-7 years (REC no. 17/EM/0083).

Recruitment: Female participants and partners of the male participants of the IOWBC (n=324) were recruited into the IOW 3rd Gen study when they became pregnant. A newsletter was sent at the beginning of the study and every 12 months, outlining briefly the aims of the research project and asking cohort members to inform us if they or their partners plan to have a baby in the next year. Female cohort mothers and partners of male cohort members are also identified from antenatal clinic bookings and invited to participate. Where possible, once pregnant women have been recruited, their respective partners were also enrolled (n=263). At the start of the study and subsequently, some IOW cohort participants informed us that they already had children. These children were also recruited into the 3rd generation study (postnatal recruits), which forms about 25% of the total 3rd Gen cohort. Assessments during pregnancy, at birth and in early infancy had been missed on these children.

How often have they been followed up?

F1-mothers have been assessed three times during early (12 and 20 weeks) and late (28-32 weeks) pregnancy. Their partners were assessed once, either during pregnancy or subsequently. At birth, placental tissue and cord blood samples were collected and detailed information was collected from the medical/maternity records. Children were then seen at the age of 3 and 6 months during a home visit. At one year, children were assessed at the research centre or at home for a full visit. At 2 years, questionnaires were completed by telephone. At 3 and 6-7 years, children were seen either at home or at the research centre. This is a dynamic cohort and children continue to be recruited as they are born into the cohort and are going through various stages of assessment. The number of cohort participants

who have been recruited so far and have had assessments at various ages are provided in figure 1. The challenge with the 3rd generation cohort is that children are recruited over years, whenever female IOWBC members or partners of male IOWBC members become pregnant. Consequently, the 3rd generation cohort includes multiple children per IOWBC women and men and also with different partners. Additionally, it means that the 3rd generation cohort children are of different ages and at different stages along their timeline of study follow-up.

What has been measured?

As shown in Table 1, we have assessed children and their parents at multiple time points. Thrice during pregnancy (early; 12 and 20 weeks, and late, 28-32 weeks) mothers completed detailed questionnaires, height and weight were measured, and blood and urine samples were obtained. Postnatally, mothers underwent skin prick tests (to common aeroallergens and food allergens) and spirometry (lung function) at the 3 month or 12-month visit. Further information was gleaned from the maternity notes and medical records including treatments such as antibiotics and mode of delivery, as well as birth weight and week of gestation.

At birth a piece of placenta (a wedge from centre to the periphery) was cut and preserved at -80° C. Cord blood samples were collected for DNA extraction for genome-wide genotyping, genome-wide DNA-methylation, a sample in RNA later for RNA extraction to allow assessment of genome-wide gene expression and a sample of serum stored for lipidomics and total IgE and cytokines analysis. We have also sought to obtain the neonatal heel prick blood samples, which are collected onto Guthrie cards, as part of the standard health assessment. DNA was extracted from the stored Guthrie cards blood spots,[8] to perform genetic and epigenetic studies in children where cord blood was not collected. Breast milk samples have been collected once at approximately 3 months after birth in mothers who were breast feeding at that time.

Children were assessed at 3 and 6 months and 1, 3 and 6-7 years with detailed questionnaires, height and weight measurement, and collection of urine sample and microbiome samples from skin, nose and faeces and stored at -80° C. Home visits were carried out at 3 months, 1, 3 and 6-7 years to collect samples of house dust from the living room and child's bedroom. Skin prick tests were carried out in children at 1, 3 and 6-7 years of age and lung function test (spirometry) was carried out at 6-7 years. At 2 years, a telephone questionnaire was completed and reported-height and weight were recorded. All fathers were contacted, either before or after the birth of the child. Those consented completed a questionnaire, underwent skin prick test and spirometry, and their height and weight were measured, and a blood sample was collected.

Questionnaires: Detailed information on pregnancy characteristics and any complications were collected (Table 2). History of allergic diseases including asthma, eczema, allergic rhinitis and food allergy was obtained from both parents during pregnancy. A brief maternal dietary questionnaire was completed using validated questionnaires[9] and information on maternal antibiotic and other drug use (such as paracetamol) was obtained twice during pregnancy. Exposure to smoking, pets, socioeconomic class, and house characteristics were recorded during pregnancy and updated at each assessment of the child. Further exposure information such as day care attendance, farm exposure, and upper and lower respiratory tract infections was also collected. At 3 months and 1 and 2 years, information on method of infant feeding and age of introduction of solid foods was recorded. For children's assessments at 3 and 6 months and 1, 2, 3 and 6-7 years, standardised ISAAC (International Study of Asthma and Allergy in Children) questionnaires were added, which sought information on wheeze, asthma, and rhinitis, and food allergy questions.

Table 1 provides a summary of data and samples collected from parents and children participating in the IOW 3rd Gen cohort. All participant data is kept at the David Hide Asthma and Allergy Centre on the Isle of Wight. Anonymized data has been transferred to the University of Southampton (UK), University of Memphis (US) and Michigan State University (US) under data transfer agreements. The secured participant data comprises the name of the mother, father, date of delivery, and contact information,

including address and mobile and landline telephone numbers, and contact information of closest relative or friend likely to know participant's whereabouts should we lose contact. This extensive database is maintained by a full-time data manager with approval from the Ethics Committee and with participant's consent.

What has been found?

Table 3 provides demographic and allergic disease information on both parents of the 3rd Gen cohort children and table 4 provides period prevalence of allergic manifestations in this cohort at various ages. As the cohort children are still going through their assessment at various ages, the numbers are different at each age.

Genome-wide genotyping and methylation assessment was conducted on mothers during pregnancy and children at birth. This data set when combined with the IOWBC data set that has been collected over 26 years, will provide an F2-generation cohort information for study of exposure and disease-related epigenetic changes and transgenerational inheritance of allergic diseases. We are also collaborating with investigators working in this area and have joined consortia with a shared interest such as PACE (Pregnancy and Childhood Epigenetics; a consortium of 28 birth cohorts).[10] These activities have resulted in a number of conference presentations and publications. Following is a summary of what has so far been reported.

A brief overview of publications

1 **Changes in DNA-methylation from age 18 to pregnancy:** Changes in DNA-methylation of Th1, Th2, Th17, and regulatory T cell pathway genes were found before and during pregnancy and these methylation changes were suggestive of involvement of both Th1 and Th2 pathways.[11]

2 **DNA-methylation during puberty, young adulthood, and pregnancy:** A higher consistency in DNA-methylation was observed during puberty (10 to 18 years) and between age 18 years to early pregnancy while there was low consistency/stability between early and late pregnancy in the same individual, indicating that pregnancy is a time of dynamic change.[12]

3 **Filaggrin gene expression at birth and eczema risk in infancy:** Filaggrin gene (*FLG*) expression in umbilical cord blood was associated with eczema development in infancy, suggesting that early identification of infants at increased risk of eczema is possible.[13]

4 **DNA-methylation associated with eczema:** In the IOWBC, 88 CpGs were associated with eczema risk of which about half showed the same direction of association with eczema risk in the 3rd Gen cohort.[14]

5 **DNA-methylation, Season of birth and allergic disease:** Twenty CpGs were associated with season of birth and allergic outcomes in the IOWBC at 18 years of age, but not replicated in the 3rd Gen cohort at birth, suggesting that changes in DNA-methylation may arise post-natally.[15]

6 **Maternal smoking in pregnancy and DNA-methylation in newborns:** Over 6,000 CpGs were differentially methylated in relation to maternal smoking and several CpGs showed persistence into later childhood.[16]

7 **Epigenome-wide association study of asthma**: Methylation at cg16658191 at age 10 was associated with adolescent asthma in the IOWBC and replicated in the cord blood in the 3rd Gen cohort with increased expression of HK1 gene predicting infant wheezing.[17]

8 **DNA-methylation trajectories during pregnancy:** 196 CpG sites displaying intra-individual longitudinal changes in DNA-methylation during pregnancy were identified.[18]

9 **Father's smoking with offspring DNA-methylation:** Six differentially methylated regions were significantly associated with paternal smoking.[19]

10 **DNA-methylation profile between paired cord blood and neonatal blood on Guthrie cards:** A large proportion (70.1%) of the CpGs agreed between the two sources.[20]

11 **Estimation of Eosinophil Cells in Cord Blood:** A Bayesian measurement error model was developed to estimate eosinophils in cord blood, where actual counts are not available.[21]

12 **Maternal dietary intake during pregnancy:** Our analysis confirmed a reduction in maternal dietary exclusion of peanut in response to recent changes in guidelines.[22]

13 **PACE Consortium contributions: A consortium of ~25 birth cohorts and ~10,000 children in collaboration with 3rd Gen cohort:**

13.1 **Maternal BMI and offspring epigenome.** A meta-analysis of 19 cohorts (n=9,340), identified associations between maternal adiposity and newborn DNA-methylation.[23]

13.2 **DNA-methylation and childhood asthma.** A cross-sectional meta-analysis identified 179 CpGs and 36 differentially methylated regions for asthma in children.[24]

13.3 **DNA-methylation associated with birthweight**: A meta-analysis of 8,825 neonates (24 cohorts), confirmed association of neonatal blood DNA-methylation with birthweight at 955 sites.[25]

What are the main strengths and weaknesses?

Strengths: This unique study has several strengths including (1) well characterised intergenerational trajectories of body mass, eczema, wheezing and asthma, (2) extensive assessments at 3 and 6 months and 1, 2, 3 and 6-7 years of age, with information obtained from patient and medical records, and (3) multigenerational data with in utero conditions plus genetic and epigenetic influences enabling study of health risk over generations. Maternal specimens (blood, serum, urine) at different gestational ages and microbiome samples from multiple sites were collected repeatedly in early life.

Weaknesses: A subset of children (n=135) were recruited postnatally and thus do not have cord blood and placenta samples. The study is intensive as it is conducting multiple assessments and seeking multiple samples from both parents and children; this means that not all assessments are performed on every child and samples are not collected from all participants on each occasion. This may result in missing information and risk of bias. However, table 4 indicates that this risk is minimal.

Can I get hold of the data? Where can I find out more?

The cohort profile is available on www.allergyresearch.org.uk. We encourage collaboration. Please contact Mr. Stephen Potter (stephen.potter@iow.nhs.uk).

Profile in a nutshell

- IOW Birth Cohort (IOWBC) is a whole-population prospective study, established in 1989-90 on the Isle of Wight, United Kingdom.
- The IOW 3rd Gen cohort comprises offspring of the IOWBC with overall data and samples on 3 successive generations; 3rd Gen cohort, their parents (IOWBC) and grandparents.
- The IOW 3rd Gen cohort was established to investigate asthma and allergic diseases across generations.
- IOWBC participants and their partners (mothers n=441, fathers n=305) and their children (n=530) were enrolled between 2010 to 2019.
- Mothers were assessed 3 times during pregnancy, fathers once and children 6 times between ages 3 months to 6 years.
- Information on asthma and allergic diseases and diet and environmental exposures has been collected.
- Samples of DNA, serum, blood, saliva, and stool, skin and nasal swabs and dust samples were collected for biomarkers, microbiome, genetic and epigenetic assessments.
- For collaboration and data access, the cohort profile is available on www.allergyresearch.org.uk.

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Figure 1: Flow diagram showing recruitment and assessment of F1 parents and F2 children. Overall, 441 mothers and 530 children were recruited. 135 (25%) mother/children pairs were recruited postnatally and in these pregnancy questionnaires were completed retrospectively. The percentages at different ages represent number of mothers /out of mothers who became pregnant) or children assessed /out of number of children who have reached that age.

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Table 1. Information and samples collected from the Isle of Wight 3rd Gen cohort

Assessments	Mothers (F1)		Fathers (F1)	3rd Gen cohort children (F2)						
Time of data collection	Pregnancy			Birth	Post-natal					
	12-20 weeks	28 weeks	Any time	0 month	3 months	6 months	1 year	2 years	3 years	6-7 years
Questionnaires	12wk = 388 20wk = 441	28wk = 340	305	-	442	194	303	202	180	82
Data from hospital notes	-	-	-	397	-	-	-	-	-	-
Height, weight, BMI	12wk = 388 20wk = 441	28wk = 340	305	-	442	194	303	202	180	82
Skin prick tests	304*	-	196	-	-	-	350	-	147	78
Lung function (Spirometry)	135*	-	93	-	-	-	-	-	-	75
Placenta pieces/samples	-	-	-	273	-	-	-	-	-	-
Blood or saliva	226	298	140	273	-	-	179	-	-	-
Urine cotinine	178	235	-	-	257	-	184	-	99	65
Breast milk	-	-	-	-	44	-	-	-	-	-
Faecal samples	-	-	-	-	207	-	193	-	56	27
Nasal secretions	-	-	-	-	244	-	228	-	137	89
Skin microbiome samples	-	-	-	-	217	-	201	-	125	89
House dust samples	-	-	-	-	263	-	-	-	79	64

Notes: BMI: Body mass index; IgE: Immunoglobulin E, DNA: Deoxyribonucleic acid

*Skin Prick Test and Spirometry performed at 3 months.

Table 2. Details of questionnaire information in the Isle of Wight 3rd Gen cohort

Assessments	Mothers (F1)		Fathers (F1)	3rd Gen cohort children (F2)						
Time of data collection	Pregnancy			Birth	Post-natal					
	12-20 weeks	28 weeks	Any time	0 month	3 months	6 months	1 year	2 years	3 years	6-7 years
Family history of atopy	x	x	x	-	x	-	x	x	x	x
Diet whilst pregnant	x	x	-	-	-	-	-	-	-	-
Infant feeding/weaning	-	-	-	-	x	x	x	x	-	-
Exposure to smoking	x	x	x	-	x	x	x	x	x	x
Exposure to pets	x	x	x	-	x	x	x	x	x	x
Socioeconomic class, house characteristics	x	x	-	-	x	-	x	-	x	x
Brief dietary questionnaire	x	x	-	-	x	x	x	x	x	x
Upper and lower RTI	-	-	-	-	x	x	x	x	x	x
Antibiotic use	x	x	-	x	x	x	x	-	x	x
Wheeze, asthma, rhinitis, food allergy	x	x	x	-	x	x	x	x	x	x
Treatment used	x	x	-	x	x	x	x	-	x	x

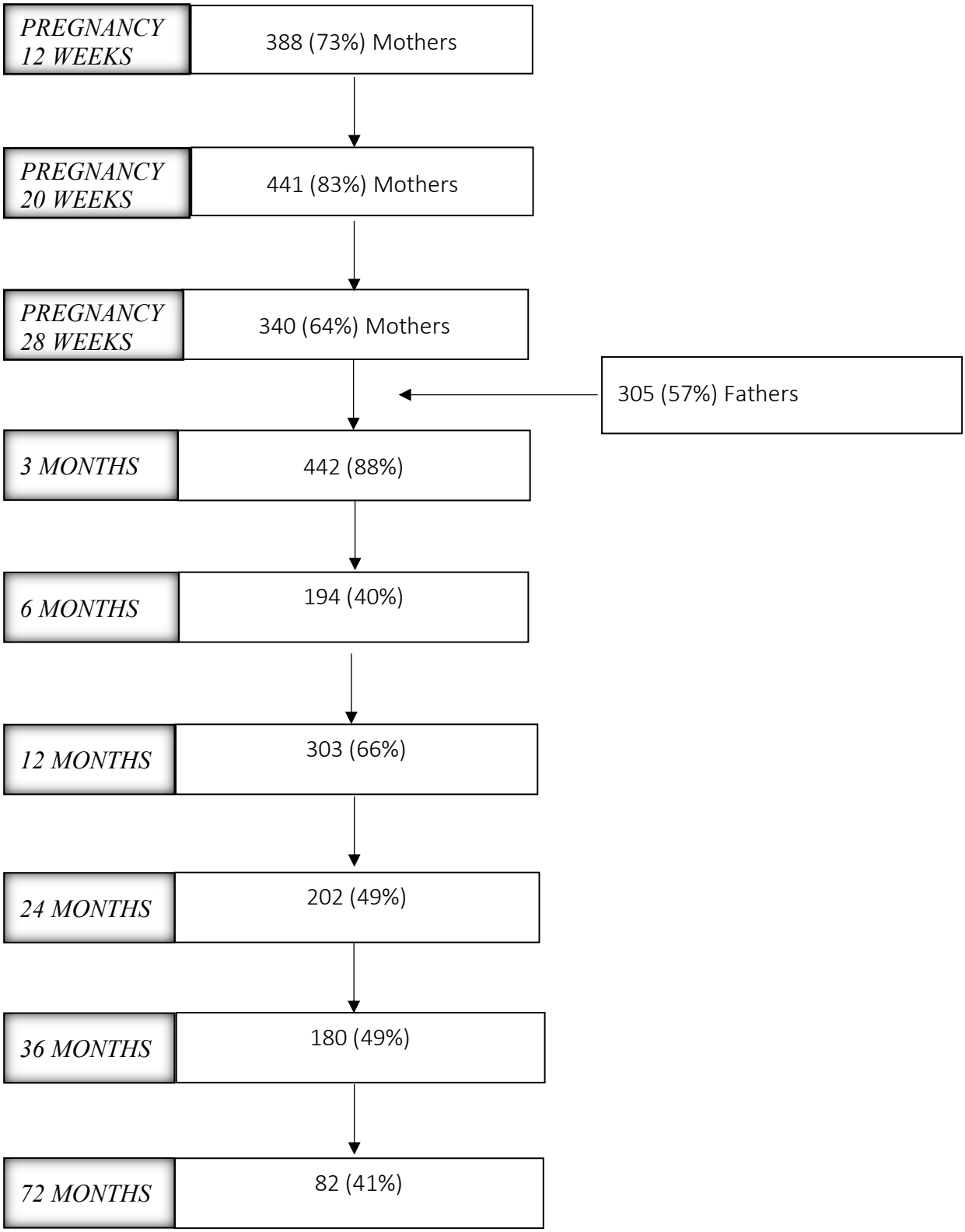
Note: RTI: Respiratory tract infection

Table 3. Demographic characteristics of the parents of the Isle of Wight 3rd Gen Cohort participants

	Mothers (study member of F1)	Fathers (study member of F1)
Mean maternal age (years)		
First birth	23.8 (n=317)	26.3 (n=231)
Second birth	25.3 (n=163)	27.7 (n=114)
Third birth	26.5 (n=48)	30.4 (n=35)
Own house	119/388 (30.7%)	87/247 (35.2%)
Gas cooker	247/388 (63.7%)	147/247 (59.5%)
Visible dampness	130/388 (33.5%)	74/246 (30.1%)
Cat ownership	127/388 (32.7%)	81/267 (30.3%)
Dog ownership	110/388 (28.4%)	68/267 (25.5%)
Living on farm	4/388 (1%)	2/247 (0.8%)
Still in education	31/440 (7%)	19/304 (6.3%)
Smoking (n)	91/441 (20.6%)	110/305 (36.1%)
Asthma (n)	160/436 (36.7%)	99/302 (32.8%)
Hay fever (n)	192/436 (44.0%)	130/305 (42.6)
Eczema (n)	170/429 (39.6%)	67/303 (22.1%)
Reported food allergy (n)	70/437 (16.0%)	26/305 (8.5%)
Skin prick test	84/304 (27.6%)	73/196 (37.2%)

Notes: Data from maternal questionnaire completed at 12 weeks of pregnancy, while skin prick test performed at infants' 3 or 12 months appointment
Paternal questionnaire and skin prick test was completed at any time, when father was available.

Figure 1: Flow diagram of study progress



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The original Cohort: The Isle of Wight birth cohort (IOWBC) is based on the Isle of Wight, which is an island off the south coast of England with a resident population of approximately 138,000. All children (n=1536) born on the Isle of Wight between 1st January 1989 and 28th February 1990 were enrolled and have been assessed 6 times since birth at age 1, 2, 4, 10, 18, and 26 years for the development of asthma and allergic diseases.

The new focus: The Isle of Wight 3rd Generation cohort (IOW 3rd Gen) was setup to study the natural history and risk factors for asthma, allergic diseases and lung function during the life course and over three generations. Genetics, epigenetics, and gene expressions and their interaction with environmental

factors including maternal diet and the skin, gut, nasal and environmental microbiome had been studied. An important focus is the role of *in-utero* exposures versus genetic inheritance to investigate intergenerational risk of asthma and allergy.

Who is left? IOW 3rd Gen cohort consists of offsprings of the Isle of Wight birth cohort. Recruitment started in 2010, with mothers continuing to be recruited as they become pregnant and children when they are born. So far, 441 mothers and 530 children (including siblings) have been recruited with children aged between 0 (not yet born) to 13 years. Mothers were seen three times during pregnancy, fathers once and children 6 times (at 3, 6, 12 months and 2, 3, and 6 years).

New measures: The IOW 3rd Gen is a prospective cohort study with asthma, allergy, and lung function phenotype and environmental and dietary data gleaned from parents/children questionnaires, clinical assessments, linkage to medical records and biological samples collected during pregnancy, at birth, and at 3, 6, and 12 months and 2, 3 and 6-7 years. Over 10,000 samples of DNA, serum, blood, saliva, stool, skin, nasal swabs and dust samples had been collected for biomarkers, microbiome, genetic and epigenetic assessments.

Unique features: The IOW 3rd Gen cohort is one of few multigenerational birth cohorts, where pregnancy and early life exposure information is available prospectively for multiple generations avoiding confounding by environment, disease or treatment in later life. Extensive phenotype and genetic data and biological samples have been collected on 3 successive generations at multiple time points, providing an opportunity to investigate intergenerational transfer of disease risk.

Reasons to be cautious: As the cohort is largely Caucasian, generalisability of its findings to other ethnic populations may be limited. IOW 3rd Gen lacks power to study some genetic and other rare exposures. However, as the IOW 3rd Gen continues to recruit IOW cohort participants as they become pregnant, the power will continue to increase. Although, it has repeated measures across frequent time points, not all participants are seen at every assessment, which leads to missing data.

Collaboration and data access: IOW 3rd Gen has wide ranging established national and international collaborations but we are keen to collaborate with other groups. Please check our access policy at: allergyresearch.org.uk.

Figure 1: Flow diagram showing recruitment and assessment of parents and children. Overall, 530 mothers/children were recruited. 135 (25%) mother/children pairs were recruited post-natally and in these subjects pregnancy questionnaires were completed retrospectively. The percentages at different ages represent number of mothers /out of mothers who became pregnant or children assessed /out of number of children who have reached that age.

Funding and competing interests: The National Institute of Allergy and Inectious Diseases and National Heart, Lung, Blood Institute, National Institute of Health (US). There are no conflict of interest.

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